A Single Compound Alternative to a Buprenorphine/Naltrexone Combination, a functional kappa opioid receptor antagonist, produces antidepressant-like effects in mice.

Abdulrahman M. Almatroudi, Stephen M. Husbands, Christopher P. Bailey and Sarah J. Bailey
Department of Pharmacy and Pharmacology, University of Bath, UK.

Introduction: Kappa-opioid receptor antagonists have a potential as novel antidepressants. However, they have a long lasting duration of action which potentially limits their use (Carroll and Carlezon 2013. J Med Chem 56: 2178-2195). Previously, we reported that buprenorphine/naltrexone (1mg/kg) combination produced a functional short-acting kappa-antagonist that was non-sedating, non-rewarding and produced antidepressant-like effects in mice. (Almatroudi *et al.* 2013. Proceedings of the British Pharmacological Society at https://bps.conference-services.net/resources/344/3654/pdf/PHARM13_0127.pdf). Administration of buprenorphine and naltrexone as a single formulation is not achievable due to their different bioavailability, which could complicate patient compliance. Therefore, BU10119 was synthesized to have the pharmacological profile of the buprenorphine/naltrexone. Here, we report the effects of BU10119 treatment on depression-related behaviours.

Methods: CD-1 male mice (8-10 weeks) were used. Injections were administered intraperitoneally (10 ml/kg). Warm water (52°C) tail withdrawal assay was used to establish blockade of U50, 488 (10mg/kg) – induced antinociception by BU10119 (1 mg/kg) (n=5). For novelty-induced hypophagia (NIH), mice were individually housed and trained for 3 days to consume condensed milk. On test days, mice were injected with saline, buprenorphine/naltrexone combination (1 mg/kg), fluoxetine (20 mg/kg) or BU10119 (1mg/kg) one hour prior to testing behaviour (n=10). In the forced swim test (FST), a 6 min swim test session was recorded and behaviour scored manually (n=10). In the NIH test, the latency to drink and consumption were recorded in the home cage (day 4) and in the novel cage (day5). Data were analysed using a two-way repeated measures mixed model analysis or single measures one-way ANOVA (Invivostat 2.3).

Results: BU10119 (1 m/kg) blocked the antinociceptive effects of U50, 488 (treatment*time $F_{(12, 60)}$ =12.57, p< 0.001). BU10119 significantly reduced tail withdrawal latency of U50 at 1, 8 and 24 h but not 48 h (p< 0.001, p< 0.001, p< 0.01 and p=0.7). In the FST, there was a significant effect of drug-treatment on swimming and immobility behaviours (swimming: $F_{(3, 36)}$=6.58, P<0.001; immobility: $F_{(3, 36)}$ =7.02, P<0.001). Post-hoc testing revealed that fluoxetine, buprenorphine/naltrexone combination and BU10119 significantly reduced the time spent immobile, compared to controls (P<0.001). In the NIH test, there was a significant effect of drug treatment on the latency to drink in the novel cage ($F_{(4, 45)}$ =9.15, P<0.001) but not consumption ($F_{(4, 45)}$ =1.25, P=0.3). Fluoxetine, buprenorphine/naltrexone, norBNI (10 mg/kg) and BU10119 significantly reduced the latency to drink in the novel cage compared with controls (P<0.01).

Conclusion: The BU10119 is a functional kappa-opioid receptor antagonist and produced antidepressant-like effects.

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